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- (54) POLY(ALPHA-1,4-D-GLUCAN) ET MELANGES POLYMERES  
THERMOPLASTIQUES LE CONTENANT
- (54) POLY(ALPHA-1,4-D-GLUCAN) AND THERMOPLASTIC  
POLYMER MIXTURES CONTAINING THE SAME

(57) The invention relates to poly( $\alpha$ -1,4-D-glucan)s with a degree of polymerisation of at least approx. 40, preferably at least approx. 50 and most preferably at least approx. 60. Plasticised poly( $\alpha$ -1,4-D-glucan)s with the aforementioned degrees of polymerisation or thermoplastic polymer mixtures containing plasticised thermoplastic poly( $\alpha$ -1,4-D-glucan)s, are especially suitable as a support matrix for active substances used in agriculture, pharmaceutical active substances and/or cosmetic active substances.

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(57) Abstract

The invention relates to poly( $\alpha$ -1,4-D-glucan)s with a degree of polymerisation of at least approx. 40, preferably at least approx. 50 and most preferably at least approx. 60. Plasticised poly( $\alpha$ -1,4-D-glucan)s with the aforementioned degrees of polymerisation or thermoplastic polymer mixtures containing plasticised thermoplastic poly( $\alpha$ -1,4-D-glucan)s, are especially suitable as a support matrix for active substances used in agriculture, pharmaceutical active substances and/or cosmetic active substances.

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## POLY(ALPHA-1,4-D-GLUCAN) AND THERMOPLASTIC POLYMER MIXTURES CONTAINING THE SAME

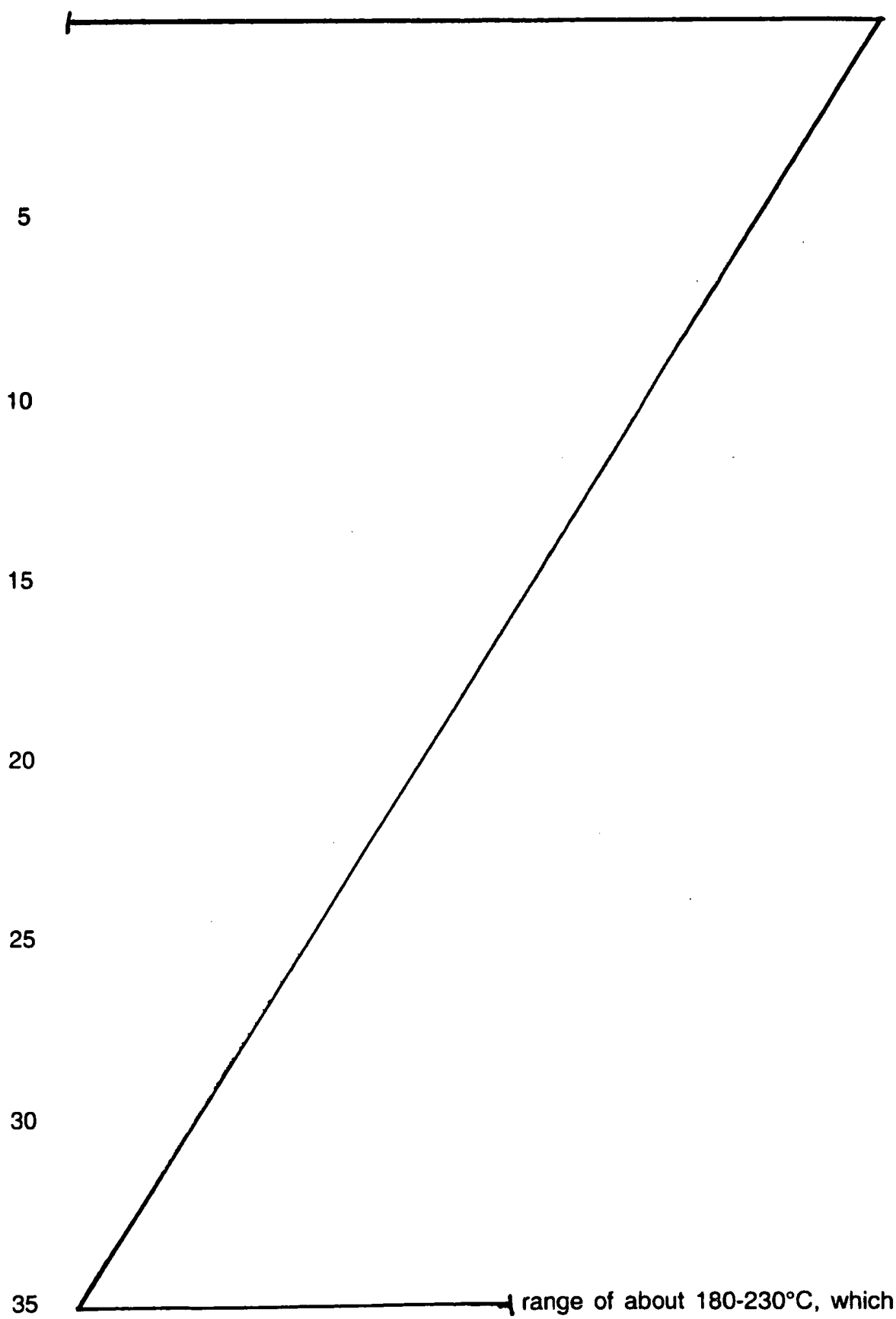
## Description

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The present invention relates to poly( $\alpha$ -1,4-D-glucan) with a degree of polymerization of at least 40, preferably 50 and even more preferably > 60, to a thermoplastic polymer mixture containing at least poly( $\alpha$ -1,4-D-glucan), to a process for preparing of a thermoplastic polymer mixture, and to a use of a thermoplastic polymer mixture containing at least poly( $\alpha$ -1,4-D-glucan) as carrier matrix for active substances such as pesticides, fungicides, insecticides, herbicides, fertilizers, pharmaceutical and/or cosmetic active ingredients, and to a process for the production of an agrochemical, pharmaceutical and/or cosmetic composition.

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The use of starch in oral pharmaceutical administration forms is documented inter alia in the Pharmacopoeia Helvetica. Besides native starch in compressed tablets, the use of thermoplastic and destructured starch is described in EP 118 240, EP 304 401, WO 89/12492, WO 90/14938 and US 5,095,054. These publications describe the strand or profile extrusion of thermoplastic formulations or polymer mixtures based on starch, and plasticizers acceptable for oral intake, such as water and the like, and preferred administration forms are disclosed. The high shear melt viscosity and the exceptional pseudoplasticity of the starch formulations leads to shear and thermal degradation of the administration forms, such as, in particular, of tablets. Degradation of the starch is mentioned in the publications mentioned in order to improve the processability. The degradation of the starch is controlled by heat, hydrogen ions or chloride ions. The resulting thermoplastic formulations are either too brittle or too tacky, depending on the proportion of low molecular weight plasticizers.

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Further publications such as WO 90/05161 and EP 0 479 964 describe thermoplastic starch (TPS) and its preparation. Thermoplastic starch, and polymer mixtures thereof, display useful mechanical properties, but the processing temperatures are usually in a range of about 180-230°C which is considerably too high for the processing of a large number of active pharmaceutical ingredients. In particular, the use described in EP 0 468 003 of thermoplastic starch in the production of pharmaceutical compositions did not have the desired result because the processing



range of about 180-230°C, which is considerably too high for the processing of a large number of pharmaceutical active ingredients. In particular, the use described in EP 0 468 003 of thermoplastic starch in the production of pharmaceutical

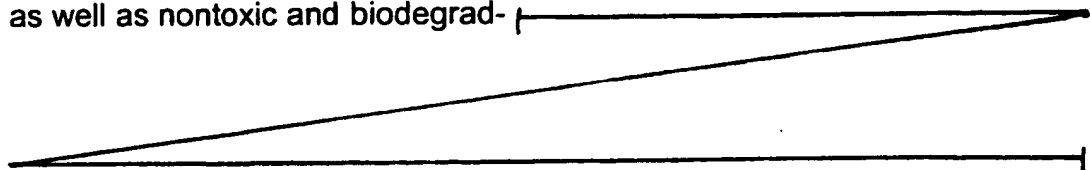
compositions did not have the desired result because the processing temperature was too high. In addition, the described thermoplastic starch is very substantially amorphous because the starch loses its potential to crystallize as a result of the thermomechanical transformation during the process of producing thermoplastic starch from native starch. As a result of the absence of crystalline fractions, the thermoplastic starch is much too hygroscopic, i.e. water is absorbed from a moist surrounding atmosphere. This is an important disadvantage because the mechanical properties of the amorphous thermoplastic starches vary widely as a result of the change in the water content.

It is therefore an object of the present invention to provide a starch-analogous material which is suitable for producing mixtures which are melt-processable and, in particular, are suitable as thermoplastic carrier substance for active substances - pesticides, fungicides, insecticides, herbicides, fertilizers, pharmaceutical and/or cosmetic active substances.

Poly( $\alpha$ -1,4-D-glucan) with a degree of polymerization of at least about 40, preferably of at least about 50 and even more preferably of at least about 60, have proved suitable for achieving the stated object, in particular on use in thermoplastic polymer mixtures containing at least said poly( $\alpha$ -1,4-D-glucan).

The degree of polymerization of the poly( $\alpha$ -1,4-D-glucan) is particularly preferably 50-56.

Linear poly( $\alpha$ -1,4-D-glucan)s are polysaccharides consisting of glucose monomers, the latter being connected together very substantially exclusively by  $\alpha$ -1,4-glycosidic linkages. The  $\alpha$ -1,4-glucan with the greatest natural occurrence is amylose, a component in vegetable starch. In the recent past, the commercial use of linear  $\alpha$ -1,4-glucans has become more and more important. As a result of its physicochemical properties, amylose can be used to produce sheets which are colorless, odorless and tasteless, as well as nontoxic and biodegrad-



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Preference is given to water-insoluble linear polysaccharides such as the polyglucan proposed by the invention, such as, for example, poly( $\alpha$ -1,4-D-glucan). In this connection, the degree of branching in position 6 is usually < 4%, preferably not more than 2%, and in particular not more than 0.5%, and the degree of branching in the other position not involved in the linear linkage, for example position 2 or 3, is, in the case of the preferred poly( $\alpha$ -

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1,4-D-glucan), preferably in each case not more than 2% and in particular not more than 1%.

5 Particularly preferred poly( $\alpha$ -1,4-D-glucans) are those having no branches or whose degree of branching is so minimal that it is undetectable by conventional methods. The prefixes " $\alpha$ " and "D" refer according to the invention solely to the linkages forming the polymer backbone and not to branches.

10 The term "water-insoluble polysaccharides" mentioned above means for the present invention poly( $\alpha$ -1,4-D-glucan)s which, according to the definition of the German Pharmacopeia, fall into the categories of compounds corresponding to classes 4 to 7 - "sparingly soluble", "slightly  
15 soluble", "very slightly soluble" and "practically insoluble". Preference is given for the present invention to slightly soluble to practically insoluble compounds, in particular very slightly soluble to practically insoluble compounds, such as, for example, slightly soluble to practically insoluble poly( $\alpha$ -1,4-D-glucan)s with a degree of polymerization  $> 40$ , preferably  
20  $> 50$ , and even more preferably  $> 60$ .

20 In the case of the poly( $\alpha$ -1,4-D-glucan)s used according to the invention, this means that at least 98% of the amount employed, in particular at least 99.5%, is insoluble in water under normal conditions ( $T = 25^{\circ}\text{C} \pm 20\%$ ,  
25  $p = 101,325 \text{ Pa} \pm 20\%$ ) (corresponding to classes 4 and 5).

25 "Very slightly soluble", corresponding to class 6, can be illustrated by the following test conditions: 1 g of the polyglucan to be investigated is heated in 1 liter of deionized water to  $130^{\circ}\text{C}$  under a pressure of 1 bar. The resulting solution remains stable for only a short time over a few minutes.  
30 The substance reprecipitates on cooling under normal conditions. After cooling to room temperature and removal by centrifugation it is possible, taking account of experimental losses, to recover at least 66% of the amount employed.

35 The preparation (isolation) of linear poly( $\alpha$ -1,4-D-glucan)s is described, for example, in WO 95/31553. In this connection there is a description of proteins which exhibit the enzymatic activity of an amylosucrase which is encoded by a DNA sequence characterized in one of claims 1 and 2 of said international patent application. These proteins are suitable for

are suitable for preparing linear poly( $\alpha$ -1,4-D-glucan)s. Further proteins with activity for the synthesis of poly( $\alpha$ -1,4-D-glucan), such as phosphorylases, glycogen synthetases, glucan transferases, starch synthetases, are suitable for preparing polyglucans for the purpose of the present invention. Likewise suitable are in vivo methods for the purpose of the present invention for preparing polyglucans by use of genetically modified organisms such as bacteria, fungi or algae, or higher plants which contain said proteins, i.e. phosphorylases, glycogen synthetases, glucan transferases, starch synthetases or amylosucrases with the activity for synthesizing polyglucans.

Poly( $\alpha$ -1,4-D-glucan) (likewise designated polyanhydro-D-glucose (PADG) in a range of the degree of polymerization (DP) of about 40-300, such as, for example, 60-100, which is preferred according to the invention, exhibits a remarkable tendency to form regular conformation, double-helix molecular morphology and high crystalline content detectable by nuclear magnetic resonance spectroscopy and X-ray diffraction. The change in the crystal structure as a result of thermal transformation is analogous to that in potato starch. The kinetics of these transformations are, however, faster than those in potato starch. The formation of molecular complexes with suitable low molecular weight mixing components such as fatty acids is coupled with the partial conformational transformation into the monohelical V structure, well known in the case of amylose, and partially into a secondary unidentified, unknown structure. The complex formation ability is approximately 3  $\times$  greater than that of amylose. The novel poly( $\alpha$ -1,4-D-glucan)s combine the ability of the two starch components - amylose and amylopectin - to form alternatively regular conformation characteristics characterizing these two components. The advantage of the low degree of polymerization of  $\alpha$ -1,4-glucans compared with that of starch (DP > 1 000), combined with the ability to form similar regular conformations like starch, leads to the use, advantageous according to the invention, as carrier substance or carrier matrix in the production of thermoplastic-based agrochemical, pharmaceutical and cosmetic formulations.

In other words, the poly( $\alpha$ -1,4-D-glucan)s proposed according to the invention combine in an advantageous manner the good processability of degraded starch and the desired properties of crystalline starch. The high crystallinity of poly( $\alpha$ -1,4-D-glucan) together with the low molecular mass of



the poly( $\alpha$ -1,4-D-glucan)s lead to a structure in which the connecting molecules lack crystallites. The connecting molecules can be introduced by adding thermoplastic starch to the poly( $\alpha$ -1,4-D-glucan). The desired volume fraction ratio of the crystalline and amorphous phase can be adjusted by mixing poly( $\alpha$ -1,4-D-glucan) and thermoplastic starch. A further aspect is the processability of plasticized starch. The ratio between the average degree of polymerization of starch and of poly( $\alpha$ -1,4-D-glucan) is preferably at least one power of 10. The limiting value of the shear viscosity at a sufficiently low shear rate is referred to as the zero shear viscosity ( $\eta(\dot{\gamma})_0$  where  $\eta$  is the viscosity and  $\dot{\gamma}$  is the shear rate). The zero shear viscosity is proportional to the weight average molecular weight to the power of 3.4. With identical parameters in terms of shear rate, plasticizer content and temperature, the shear viscosity of the thermoplastic starch is more than 1000 times higher than that of poly( $\alpha$ -1,4,-D-glucan). The consequence is a further essential aspect of the present invention, since mixtures of thermoplastic starch with plasticized poly( $\alpha$ -1,4-D-glucan) result in a considerable improvement in processability. In addition, such mixtures have advantageous mechanical properties.

Thus, for example, thermoplastic mixtures of one part of poly( $\alpha$ -1,4-D-glucan) with 3 parts of thermoplastic starch show an increase of 6 to 7 times in the elongation at break and an increase of 2 to 3 times in the energy at break compared with the corresponding values for pure thermoplastic starch. The shear rate-dependent shear viscosity of the same mixture is a factor of 2 lower at the processing temperature of the thermoplastic starch than that of the thermoplastic starch itself.

The mixture of one part of thermoplastic starch and three parts of poly( $\alpha$ -1,4-D-glucan) still shows the same energy at break as does thermoplastic starch, but the shear rate-dependent shear viscosity is a factor of more than 10 lower than that of thermoplastic starch.

The melt processability of poly( $\alpha$ -1,4-D-glucan) is an important feature of the present invention. The regular geometry of shaped articles produced by extrusion of the active substance/thermoplastic poly( $\alpha$ -1,4-D-glucan) mixture assists the control of release of active substances, for example the release of medicament; the swelling time, the disintegration time and the dissolving time of these shaped particles define the release time of the

active substance. The thermoformed parts or particles thereof must be small enough for said kinetic process to show a standard deviation which is less than the corresponding averages. The uniform homogeneous distribution of the active substance in the polymer melt can be simplified by counter-rotating twin-screw extruders provided with suitable mixing elements. In conclusion, it can be stated that this is now possible because all the necessary requirements are sufficiently met:

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10 - plasticized poly( $\alpha$ -1,4-D-glucan) can be prepared for example by the use of glycerol as plasticizer;

~~glycerol is on the list of physiologically acceptable additives for pharmaceutical formulations;~~

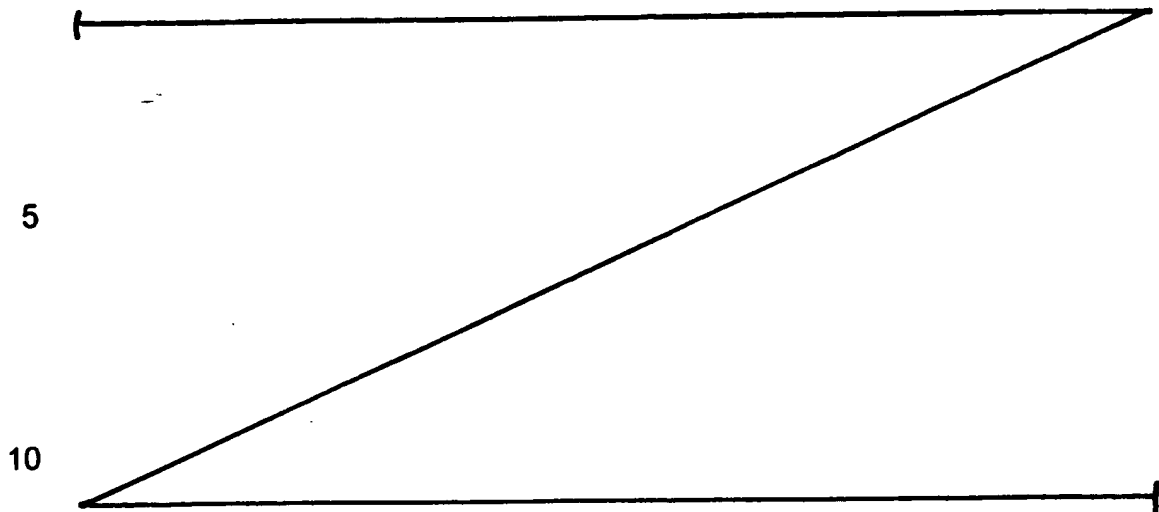
15 - the processing temperature of thermoplastic starch can be reduced through the addition of poly( $\alpha$ -1,4-D-glucan), by at least 40°C.

20 One variant of the present invention proposes a thermoplastic polymer mixture in which the content of starch such as, in particular, thermoplastic starch is between 20 and 80% by weight based on the polymer content, including polyglucan and, where appropriate, other melt-processable polymers.

25 A further variant proposes in turn a thermoplastic polymer mixture where the content of poly( $\alpha$ -1,4-D-glucan) is 20-80% by weight based on the polymer content, including the starch and, where appropriate, other melt-processable polymers.

30 On the basis of the preconditions described above, it is possible according to the present invention to mix poly( $\alpha$ -1,4-D-glucan) with thermoplastic starch and employ it in particular for the production of a thermoplastic carrier matrix, for example for agrochemical, pharmaceutical and/or cosmetic active substances.

35 An active substance is regarded for the purpose of this invention as being any bioactive substance and substance combination in the widest sense, preferably pharmaceutical active substances or agrochemical active substances which can be employed in agriculture, horticulture and forestry.



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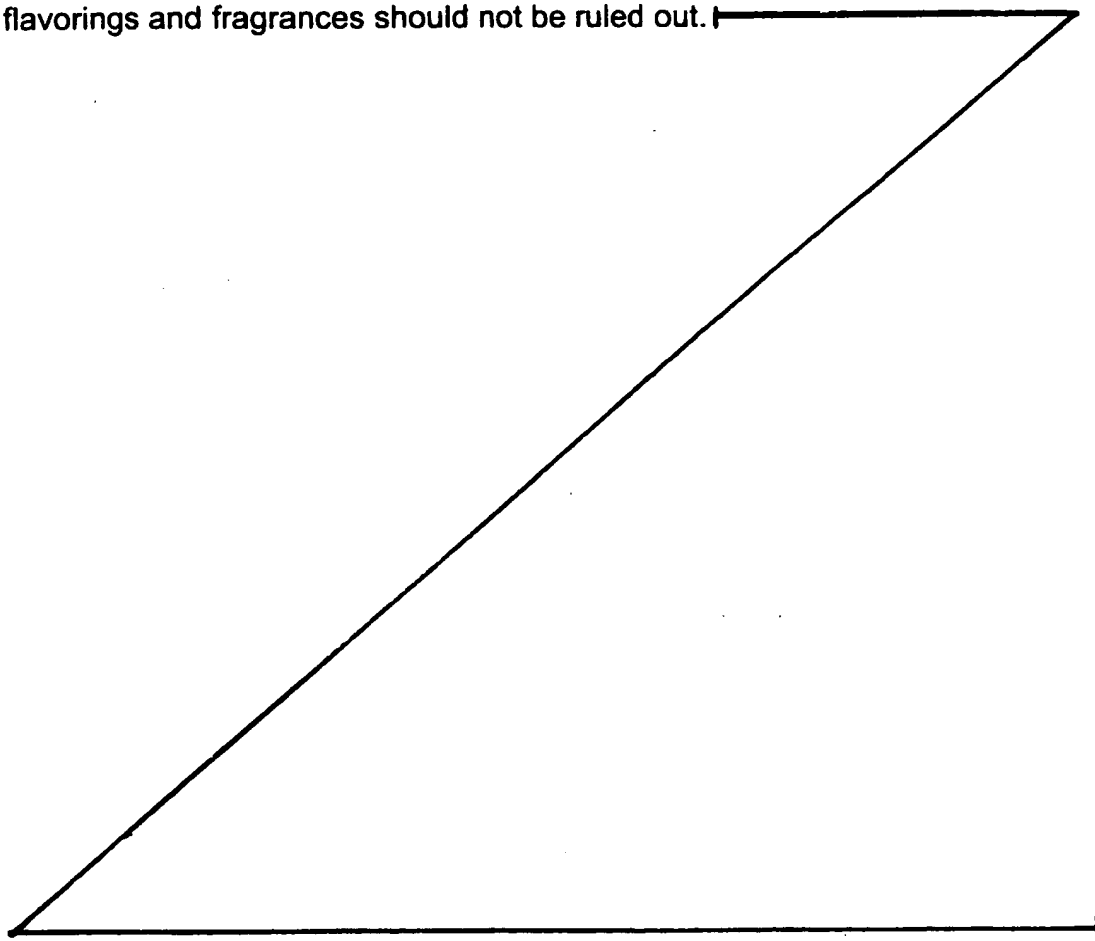
35 Besides thermoplastic starch it is also possible to employ chemically or physically modified starches. In a preferred embodiment of the present invention, the thermoplastic starch can be prepared by mixing native starch

or a starch derivative with a plasticizer in the melt with a water content of < 5% by weight based on the starch/plasticizer mixture.

5 Plasticizers include according to the invention for example the substances in the following list: sorbitol, glycerol and its oligomers and condensation products, DMSO, succinic acid, citric acid monohydrate, maleic acid and/or tartaric acid.

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15 The term agrochemical covers fertilizers, herbicides, fungicides, insecticides, pesticides and other crop protection and pest-control compositions, stored-products protection compositions, plant growth promoters and inhibitors, ensiling agents, preservatives and soil improvers. Even animal feed additives, animal hygiene and medicinal products or flavorings and fragrances should not be ruled out.



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It is possible to employ, for example, known active substances like those described, for example, in Weed Research 26, 441-445 (1986) or "The

10 Pesticide Manual", 1st edition, The British Crop Protection Council and the Royal Soc. of Chemistry, 1997 and literature cited therein. Known herbicides which can be introduced into the active substance carrier of the invention and which should be mentioned are, for example, the following active substances (note: the compounds are referred to either by the

15 "common name" of the International Organization for Standardization (ISO) or by the chemical name, where appropriate together with a conventional code number): atrazine; metolachlor; propiconazole; metalaxyl; dicamba (products, brands and trademarks of Novartis); bensulfuron; nicosulfuron; methomyl; flusilazole; benomyl (products, brands and trademarks of

20 DuPont); glyphosate; alachlor, acetochlor; butachlor; triallate (products, brands and trademarks of Monsanto); paraquat; L-cyhalothrin; fluazifop; cypermethrin; EPTC (products, brands and trademarks of Zeneca); fenoxaprop; deltamethrin; phenmedipham; endosulfan; glufosinate (products, brands and trademarks of AgrEvo); imidaciloprid; tebuconazole;

25 metamitron; metribuzin; methamidophos (products, brands and trademarks of Bayer); imazethapyr; pendimethalin; imazaquin; terbufos; imazapyr (products, brands and trademarks of Cyanamid); chlorpyrifos; trifluralin; fluroxypyr; clopyralid; haloxyfop (products, brands and trademarks of DowElanco); aldicarb; iprodione; dinufenican; bromoxynil; foseethyl-Al

30 (products, brands and trademarks of Rhône Poulenc); bentazone; epoxiconazole; sethoxydim; hormones; metazachlor (products, brands and trademarks of BASF);

acetochlor; acifluorfen; aclonifen; AKH 7088, i.e. [[[1-[5-[2-chloro-4-(trifluoromethyl)phenoxy-2-nitrophenyl]-2-methoxyethylidene]-amino]-oxy]-

35 acetic acid and -acetic acid methyl ester; alachlor; alioxydim; ametryn; amidosulfuron; amitrioi; AMS, i.e. ammonium sulfamate; anilofos; asulam; atrazin; azimsulfurone (DPX-A8947); aziprotryn, azoxystrobin; barban; BAS 516 H, i.e. 5-fluoro-2-phenyl-4H-3,1-benzoxazin-4-one; benazolin; benfluralin; benfuresate; bensulfuron-methyl; bensulide; bentazone;

benzofenap; benzofluor; benzoylpropethyl; benzthiazuron; bialaphos;  
bifenox; bromacil; bromobutide; bromofenoxim; bromoxynil; bromuron;  
buminafos; busoxinone; butachlor; butamifos; butenachlor; buthidazole;  
butralin; butylate; cafenstrole (CH-900); carbetamide, cafentrazone  
5 (ICI-A0051); CDAA, i.e. 2-chloro-N,N-di-2-propenylacetamide; CDEC, i.e.  
2-chloroallyl diethyldithiocarbamate; chlomethoxyfen; chloramben;  
chlorazifop-butyl, chlormesulon (ICI-A0051); chlorbromuron; chlorbufam;  
chlorfenac; chlorflurecol-methyl; chloridazon; chlorimuron ethyl;  
chlornitrofen; chlorotoluron; chloroxuron; chlorpropham; chlorsulfuron;  
10 chlorthaldimethyl; chlorthiamid; cinmethylin; cinosulfuron; clethodim;  
clodinafop and its ester derivatives (for example clodinafop-propargyl);  
clomazone; clomeprop; cloproxydim; clopyralid; cumyluron (JC 940);  
cyanazine, cycloate, cyclosulfamuron (AC 104); cycloxydim; cycluron;  
cyhalofop and its ester derivatives (for example butyl ester, DEH-112);  
15 cyperquat; cyprazine; cyprazole; daimuron; 2,4-DB; dalapon;  
desmedipham; desmetryn; di-allate; dicamba; dichlobenil; dichlorprop,  
diclofop and its esters such as diclofop-methyl; diethatyl; difenoxuron;  
difenzoquat; diflufenican; dimefuron; dimethachlor; dimethametryn;  
dimethenamide (SAN-582H); dimethazone, clomazon; dimethipin;  
20 dimetrasulfuron, dinitramine; dinoseb; dinoterb; diphenamide; dipropetryn;  
diquat; dithiopyr; diuron; DNOC; eglinazine-ethyl; EL 77, i.e. 5-cyano-1-  
(1,1-dimethylethyl)-N-methyl-1H-pyrazole-4-carboxamide; endotal; EPTC;  
esprocarb; ethalfluralin; eihametsulfuron-methyl; ethidimuron; ethiozin;  
ethofumesate; F5231, i.e. N-[2-chloro-4-fluoro-5-[4-(3-fluoropropyl)-4,5-  
25 dihydro-5-oxo-1H-tetrazol-1-yl]phenyl]ethanesulfonamide; ethoxyfen and  
its esters (for example ethyl ester, HN-252); etobanzanid (HW 52);  
fenoprop; fenoxan, fenoxaprop and fenoxaprop-P and their esters, for  
example fenoxaprop-P-ethyl and fenoxaprop-ethyl; fenoxydim; fenuron;  
flampropmethyl; flazasulfuron; fluazifop; fluazifop-P and their esters, for  
30 example fluazifop-butyl and fluazifop-P-butyl; fluchloralin; flumetsulam;  
flumeturon; flumiclorac and its esters (for example pentyl ester, S-23031);  
flumioxazin (S-482); flumipropyn; flupoxam (KNW-739); fluorodifen;  
fluoroglycofen-ethyl, flupropacil (USIC-4243); fluridone; flurochloridone;  
fluroxypry; flurtamone; fomesafen; fosamine; furyloxyfen; glufosinate;  
35 glyphosate, halosafen; halosulfuron and its esters (for example methyl  
ester, NC-319); haloxyfop and its esters; haloxyfop-P (= R-haloxyfop) and  
its esters; hexazinone; imazamethabenz-methyl; imazapyr; imazaquin and  
salts such as the ammonium salt; imazethamethapyr; imazethapyr;  
imazosulfuron; imidacloprid; ioxynil; isocarbamid; isopropalin; isoproturon;

isouron; isocaben; isoxapyrifop; karbutilate, kresoxim; kresoxim-methyl;  
KTU 3616; lacofen; lenacil; linuron; MCPA; MCPB; mecoprop; mefenacet;  
mefluidid; metamitron; metazachlor-, methabenzthiazuron; metham;  
methazole; methoxyphenone; methylmymron; metabenzuron; metho-  
5 benzuron; metobromuron; metolachlor; metosulam (XRD 511); metoxuron;  
metribuzin; metsulfuron-methyl; MH; molinate; monalide; monocarbamide  
dihydrogensulfate; monolinuron; monuron; MT 128, i.e. 6-chloro-N-(3-  
chloro-2-propenyl)-5-methyl-N-phenyl-3-pyridazinamine; MT-5950, i.e.  
N-[3-chloro-4-(1-methylethyl)phenyl]-2-methylpentanamide; naproanilide;  
10 napropamide; naptalam; NC 310, i.e. 4-(2,4-dichlorobenzoyl)-1-methyl-5-  
benzyloxy-pyrazole; neburon; nicosulfuron; nipyraclorfen; nitralin; nitrofen;  
nitrofluorfen; norflurazon; orbencarb; oryzalin; oxadiargyl (RP-020630);  
oxadiazon; oxyfluorfen; paraquat, pebulate-, pendimethalin; perfluidone;  
phenisophem; phenisopharm; phenmedipharm; picloram; piperophos;  
15 piributicarb; pirifenop-butyl; pretilachlor; primisulfuron-methyl; procayzine;  
prodiamine, profluraline; proglinazine-ethyl; prometon; prometryn;  
propachlor; propanil; propaquizafop and its esters; propazine; propham;  
propisochlor; propyzamide; prosulfalin; prosulfocarb; prosulfuron  
(CGA-152005); prynachlor; pyrazolate, pyrazon;  
20 pyrazosulfuron-ethyl; pyrazoxyfen; pyridate; pyrithiobac (KIH-2031);  
pyroxofop and its esters (for example propargyl ester); quinclorac;  
quinmerac; quinofof and its ester derivatives, quizalofop and quizalofop-P  
and their ester derivatives, for example quizalofop-ethyl; quizalofop-P-  
tefuryl and -ethyl; renriduron; rimsulfuron (DPX-E 9636); S 275, i.e. 2-[4-  
25 chloro-2-fluoro-5-(2-propylnyloxy)phenyl]-4,5,6,7-tetrahydro-2H-indazole;  
secbumeton; sethoxydim; siduron; simazine; simetryn; SN 106279, i.e.  
2-[[7-[2-chloro-4-(trifluoromethyl)phenoxy]-2-naphthalenyl]oxy]propanoic  
acid and methyl ester; sulfentrazon (FMC-97285, F-6285); sulfazuron;  
sulfometuron-methyl; sulfosate (ICI-A0224); TCA; tebutam (GCP-5544);  
30 tebuthiuron; Ierbacil; terbucarb; terbuchlor; terbumeton; terbuthylazine;  
terbutryn; TFH 450, i.e. N,N-diethyl-3-[(2-ethyl-6-methylphenyl)sulfonyl]-  
1H-1,2,4-triazole-1-carboxamide; thenylchlor (NSK-850); thiazafluron;  
thiazopyr (Mon-13200); thidiazimin (SN-24085) thifensulfuron-methyl;  
thiobencarb; tiocarbazil; tralkoxydim; tri-allate; triasulfuron; triazofenamide;  
35 tribenuron-methyl; triclopyr; tridiphane; trietazine; trifluralin; triflusulfuron  
and esters (for example methyl ester, DPX-66037); trimeturon; tsitodef;  
vernolate; WL 11 0547, i.e. 5-phenoxy-1-[3-(trifluoromethyl)phenyl]-1H-  
tetrazole; UBH-509; D-489; LS 82-556; KPP-300; NC-324; NC-330;

KH-218; DPX-N8189; SC-0774; DOWCO-535; DK-8910; V-53482; PP-600, MBH-001; KIH-9201; ET-751; KIH-6127 and KIH-2023.

Suitable pharmaceutical active substances are, inter alia:

- 5
- nicotine
  - scopolamine or L-hyoscine
  - hormones, for example estrogen derivatives such as estradiol; gestagen derivatives such as levonorgestrel or norethisterone acetate;
  - 10 testosterone
  - glycerol trinitrate
  - synthetic opioid analgesics such as, for example, fentanyl
  - non-steroidal antiinflammatory drugs such as, for example, flurbiprofen, diclofenac, ketoprofen, ketorolac,
  - 15 - hypotensive active substances, in particular  $\alpha$ -adrenoceptor agonists such as clonidine, in particular also so-called  $\beta$ -blockers such as propranolol, mepindolol inter alia
  - peptides such as insulin, leuprolide, enkephalin, oxytocin, ramorelix, calcitonin, buserelin and derivatives thereof
  - 20 - camphor
  - ethanol
  - cytostatics such as, for example, 5-fluorouracil
  - agents for treating parkinsonism, in particular monoamine oxidase inhibitors such as selegiline, in particular also dopamine D<sub>2</sub> agonists, in
  - 25 particular also parasympathomimetics, specifically cholinesterase inhibitors such as physostigmine
  - neuroleptics

Potential active substances for oral use are, for example:

- 30
- $\beta$ -receptor blockers such as, for example, metoprolol, acebutolol, atenolol inter alia
  - antiparkinson agents such as, for example, levodopa, benserazide, biperiden or combinations of various antiparkinson agents
  - 35 - calcium channel blockers such as, for example, nifedipine, diltiazem inter alia
  - ACE inhibitors such as, for example, captopril, lisinopril, perindopril inter alia
  - opioids and opioid analgesics such as, for example, morphine sulfate



- antiallergics such as, for example, terfenadine, loratadine inter alia
- antiarrhythmics such as, for example, mexitil
- antiepileptics such as, for example, carbamazepine
- antiinflammatory drugs such as, for example, piroxicam, indomethacin
- 5 - theophylline and derivatives as bronchospasmolytic
- diuretics such as, for example, furosemide, piretanide
- antigout agents such as, for example, allopurinol
- lipid-lowering agents such as, for example, clofibrate, lovastatin
- antidepressants such as, for example, amitriptyline.

10

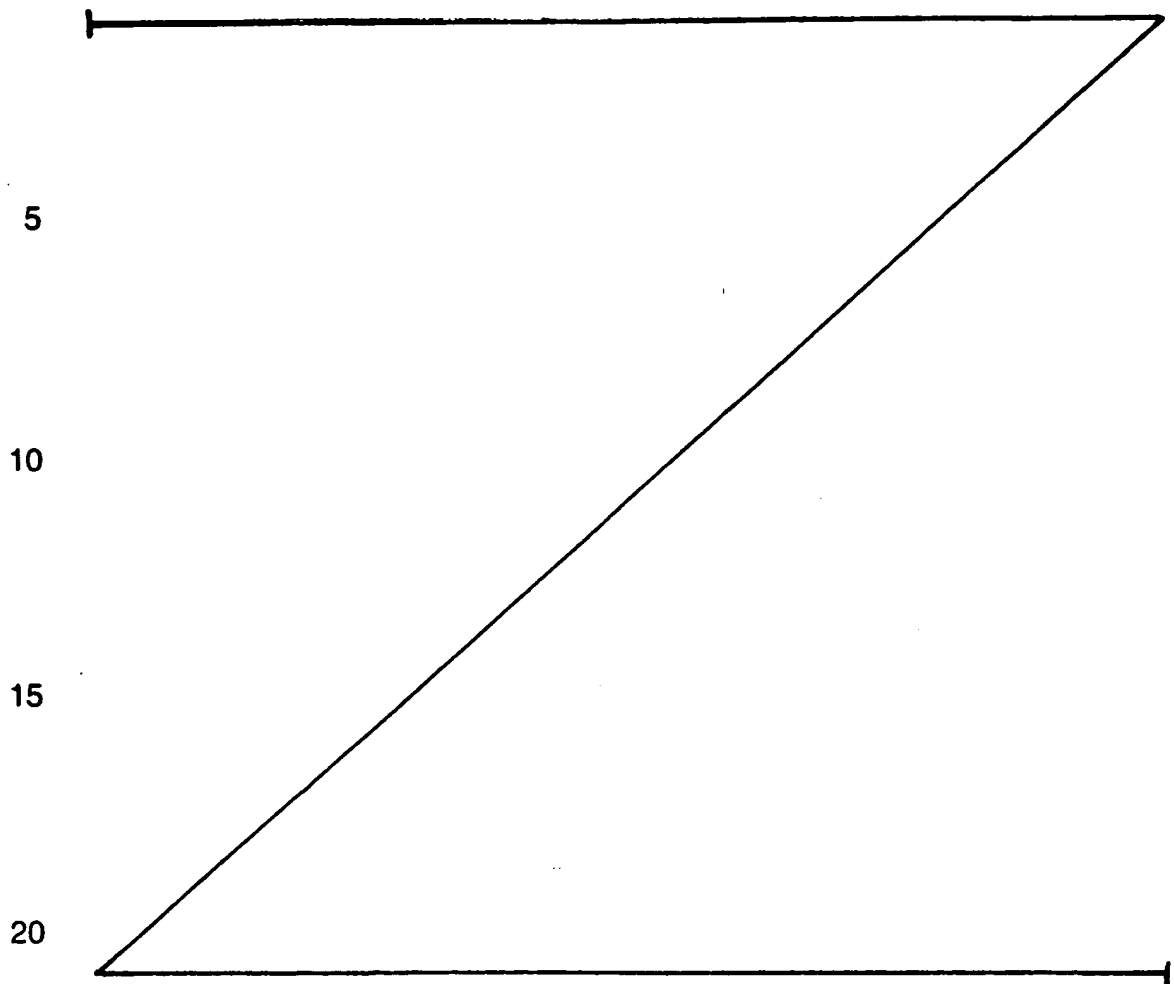
The active substances mentioned in the above list are, of course, only examples to illustrate the present invention in detail.

15 Both poly( $\alpha$ -1,4-D-glucan) and the aforementioned thermoplastic mixtures of poly( $\alpha$ -1,4-D-glucan) with thermoplastic starch can, of course, be mixed with other melt-processable polymers, which are preferably biocompatible, as well as preferably physiologically tolerated. Possible examples thereof are vinyl compounds such as ethylene/vinyl alcohol and copolymers of vinyl acetate and vinyl acrylate with ethylene. Other suitable polymers are,  
20 for example, polyalkanoates such as, in particular, aliphatic polyesters.

~~It is also possible for  $\alpha$ -1,4-glucan to be complexed, such as, for example, with palmitic acid. The complexation can also be used where appropriate to bind pharmaceutical, cosmetic, agricultural and similar active substances to poly( $\alpha$ -1,4-D-glucan) by complexation. It is proposed in this connection to mix the poly( $\alpha$ -1,4-D-glucan) with between 2 and 20% by weight of a complexing agent.~~

25

The invention is now explained in detail below by means of examples, it  
30 being self-evident that the present invention is not confined to the examples mentioned.



It is also possible for  $\alpha$ -1,4-glucan to be complexed, such as, for example, with palmitic acid. The complexation can also be used where appropriate to bind pharmaceutical, cosmetic, agricultural and similar active substances to poly( $\alpha$ -1,4-D-glucan) by complexation. It is proposed in this connection to mix the poly( $\alpha$ -1,4-D-glucan) with between 2 and 20% by weight of a complexing agent.

A preferred embodiment of the present invention makes available a process in which a thermoplastic polymer mixture is prepared by initially melting poly( $\alpha$ -1,4-D-glucan) and adding to the latter at least 20% by weight, preferably at least 30% by weight, of a plasticizer at about 170°C.

It is particularly preferred in this process for the molten and plasticized poly( $\alpha$ -1,4-D-glucan) to be mixed with at least one other melt-processable polymer in the melt at a temperature in the range from about 140 to 180°C, the mixing in the melt preferably taking place in an extruder, the residence time in the extruder being 1 to 5 min at 50 to 200 revolutions per minute,

- antiallergics such as, for example, terfenadine, loratadine inter alia
- antiarrhythmics such as, for example, mexilitil
- antiepileptics such as, for example, carbamazepine
- antiinflammatory drugs such as, for example, piroxicam, indomethacin
- 5 - theophylline and derivatives as bronchospasmolytic
- diuretics such as, for example, furosemide, piretanide
- antigout agents such as, for example, allopurinol
- lipid-lowering agents such as, for example, clofibrate, lovastatin
- antidepressants such as, for example, amitriptyline.

10

The active substances mentioned in the above list are, of course, only examples to illustrate the present invention in detail.

15

Both poly( $\alpha$ -1,4-D-glucan) and the aforementioned thermoplastic mixtures of poly( $\alpha$ -1,4-D-glucan) with thermoplastic starch can, of course, be mixed with other melt-processable polymers, which are preferably biocompatible, as well as preferably physiologically tolerated. Possible examples thereof are vinyl compounds such as ethylene/vinyl alcohol and copolymers of vinyl acetate and vinyl acrylate with ethylene. Other suitable polymers are,

20

for example, polyalkanoates such as, in particular, aliphatic polyesters.

25

It is also possible for  $\alpha$ -1,4-glucan to be complexed, such as, for example, with palmitic acid. The complexation can also be used where appropriate to bind pharmaceutical, cosmetic, agricultural and similar active substances to poly( $\alpha$ -1,4-D-glucan) by complexation. It is proposed in this connection to mix the poly( $\alpha$ -1,4-D-glucan) with between 2 and 20% by weight of a complexing agent.

30

The invention is now explained in detail below by means of examples, it being self-evident that the present invention is not confined to the examples mentioned.

**Examples 1 to 7:**

To investigate the suitability of mixtures of poly( $\alpha$ -1,4-D-glucan) with thermoplastic starch, the entire series of mixtures of poly( $\alpha$ -1,4-D-glucan) and thermoplastic starch was investigated for crystallinity and mechanical properties. The plasticizer used for poly( $\alpha$ -1,4-D-glucan) was 35% glycerol, because this material has proved very suitable and, moreover, as already mentioned above, this material can be employed acceptably in pharmaceutical and/or cosmetic preparations. Poly( $\alpha$ -1,4-D-glucan) is in this case mixed with the plasticizer, such as the glycerol mentioned, at about 170°C. The poly( $\alpha$ -1,4-D-glucan) plasticized in this way is then mixed with thermoplastic starch, once again at a temperature in the range from about 160° to 180°C, in an extruder, the residence time being between 1 and 5 minutes depending on the composition, at 50 to 200 revolutions per minute, preferably 100 rpm. The plasticizing and mixing work introduced to the extruder is between 0.2 and 0.4 kWh per kg of poly( $\alpha$ -1,4-D-glucan).

The thermoplastic starch used to prepare the mixtures with poly( $\alpha$ -1,4-D-glucan) was prepared by mixing with a plasticizer such as, for example, with 35% glycerol at a temperature in the range from about 160°C to 180°C, the essential feature for the preparation of the thermoplastic starch now being a reduction in the water content in the melt to at least less than 5% by weight based on the starch/plasticizer mixture during the mixing process. Otherwise, reference is made to European patent EP 0 397 819, which is derived from WO 90/05161 mentioned at the outset, for the preparation of the thermoplastic starch.

However, it is also possible alternatively to prepare the thermoplastic mixtures between poly( $\alpha$ -1,4-D-glucan) and thermoplastic starch in one step by melting poly( $\alpha$ -1,4-D-glucan) and native starch together with 35% glycerol in an extruder at about 170°C and molding, it being necessary once again for the production of the thermoplastic starch to remove moisture from the melt to a value below 5% by weight based on the amount of native starch and proportionate to the amount of plasticizer such as, for example, 35% glycerol added to the starch.

To determine the crystallinity, various samples differing in composition were investigated three days after preparation by x-ray diffraction, the crystalline content  $A_c$  in the X-ray spectrum then being separated from the

amorphous halo  $A_a$  in the resulting spectra, and the degree of crystallinity  $C$  being calculated in percent in accordance with the following formula

$$C = 100 \times A_c / (A_a + A_c).$$

5

The crystallinity for the series of mixtures based on the weight fraction of poly( $\alpha$ -1,4-D-glucan) with in each case a weight fraction of glycerol as plasticizer of 0.35 is indicated in table 1.

10 Setting the crystallinity of 45.8% for pure poly( $\alpha$ -1,4-D-glucan) equal to 1 and relating the crystallinity of the other samples thereto results in an almost linear relation between the relative crystallinity and the proportion of poly( $\alpha$ -1,4-D-glucan). The numerical series indicated above is also shown in figure 1 of the appended figures.

15

Poly( $\alpha$ -1,4-D-glucan) thus causes no increase in the crystallinity of the thermoplastic starch phase and, conversely, the TPS content brings about no decrease in the crystallinity of poly( $\alpha$ -1,4-D-glucan). The structure found is a mixture of V amylose and an as yet unidentified structure, concerning which reference is made to figure 2.

20

The mechanical properties of the series of mixtures between poly( $\alpha$ -1,4-D-glucan), plasticized with 35% glycerol and thermoplastic starch, were also measured, resulting in the following values:

25

Table 1

Poly( $\alpha$ -1,4-D-glucan) weight fractions	E MPa	$\delta_m$ MPa	$\epsilon_b$ %	C %	
Example 1	1.00	52.7+/-7	2.8+/-0.5	11.7+/-2	0.458
Example 2	0.875	55.3+/-9	4.5+/-0.5	21.1+/-3	0.386
Example 3	0.75	46.2+/-6	5.6+/-0.7	26.2+/-5	0.382
Example 4	0.62	31.3+/-1	4.0+/-0.1	23.8+/-1	0.285
Example 5	0.50	18.1+/-2	3.5+/-0.2	42.0+/-7	0.247
Example 6	0.25	24.2+/-7	4.6+/-0.4	79.0+/-6	0.072
Example 7	0	184+/-34	9.4+/-0.5	15.8+/-5	0.045

30 Five tensile tests were carried out on each sample. The changes in strength and elongation at break are depicted in figure 3, stating the

poly( $\alpha$ -1,4-D-glucan) content. Within the series of mixtures, the strength is at a maximum at 9.4 MPa with pure thermoplastic starch, after which it rapidly declines and reaches a minimum at 3.5 MPa for 50% of  $\alpha$ -1,4-glucan, which is only slightly above the strength of 2.8 MPa for pure poly( $\alpha$ -1,4-D-glucan). After this minimum, the strength increases again and reaches an intermediate maximum at 75% poly( $\alpha$ -1,4-D-glucan) in order to decline again thereafter up to 100% poly( $\alpha$ -1,4-D-glucan). Such an S-shaped strength profile is customary, and this behavior can be observed in many series of mixtures. The energy at break with a TPS content of 25% is comparable with pure thermoplastic starch. The modulus of elasticity for 100% TPS with 35% glycerol is 184 MPa, and it then falls to about 20 MPa at 50% poly( $\alpha$ -1,4-D-glucan) in order to rise again thereafter to about 50 MPa for pure poly( $\alpha$ -1,4-D-glucan). TPS and poly( $\alpha$ -1,4-D-glucan) are comparable in relation to elongation at break. However, a poly( $\alpha$ -1,4-D-glucan) content of 25% distinctly improves the elongation at break to 79%.

As already mentioned above, glycerol is a suitable plasticizer for poly( $\alpha$ -1,4-D-glucan) and it is possible to achieve, for example by using 35% glycerol, properties virtually identical to those in thermoplastic starch, likewise plasticized with 35% glycerol. However, it is possible in principle to use for example for plasticizing poly( $\alpha$ -1,4-D-glucan) all materials which are likewise suitable for plasticizing thermoplastic starch. Suitable examples are glycerol, DMSO, citric acid monohydrate, sorbitol etc., to mention only a few. In general, all substances with a solubility parameter of greater than 30 MPa<sup>0.5</sup> are suitable, and they must be physiologically acceptable in the range of pharmaceutical applications. In particular, use of 35% citric acid monohydrate resulted in a material with astonishing mechanical properties. Thus, for example, a modulus of elasticity of 550 MPa and a strength of 15 MPa with an elongation at break of 15% were found.

#### **Production of pharmaceutical and cosmetic compositions:**

The basis initially started from again is plasticized poly( $\alpha$ -1,4-D-glucan) as previously prepared by the process described in connection with examples 1 to 7. A thermoplastic polymer mixture suitable as carrier matrix for agrochemical, pharmaceutical and/or cosmetic active substances can be prepared by using either mixtures between the plasticized poly( $\alpha$ -1,4-D-glucan) and thermoplastic starch or else mixtures between the polyglucan and other suitable polymers such as vinyl compounds, polyalkanoates, to

mention only a few. It is, of course, essential in this connection that these other polymers are melt-processable, physiologically tolerated and, preferably, biocompatible. It is, of course, also possible to use mixtures between polyglucan, thermoplastic starch and other polymers to prepare said carrier matrix. The sequence of mixing the components to prepare the thermoplastic polymer mixture can be chosen freely per se, i.e. it is possible to start with the thermoplastic starch, to which the plasticized polyglucan is added, or else with a polymer mixture of another polymer with the thermoplastic starch, to which the polyglucan is added in the extruder etc.

Finally, to produce the agrochemical, pharmaceutical and/or cosmetic composition, one or more agrochemical or pharmaceutical or cosmetic active substance(s), and other physiologically tolerated additives, fillers and the like, are added to the melt of said thermoplastic polymer mixture. It is essential in this connection that the temperature in the extruder or when mixing in the melt is not chosen to be too high, so that no damage to the pharmaceutical or cosmetic active substance can occur.

#### 20 **Example 8: Production of a transdermal therapeutic system**

To produce an amylose film which has a transdermal therapeutic system as constituent, initially one part of poly( $\alpha$ -1,4-D-glucan) is mixed with two parts of thermoplastic starch in the melt in an extruder at about 170°C, each of the two materials containing 35% glycerol as plasticizer. The polymer melt is then cooled to about 140°C, and nicotine as pharmaceutical active substance, and about 5% water, are added and then the resulting pharmaceutical polymer melt is extruded to sheets with a thickness of 200  $\mu$ . The nicotine dosage is such that 7 cm<sup>2</sup> cut out of the extruded film normally contain about 35 mg of nicotine. As a rule, the amylose film obtained in this way is not used directly to test the release; on the contrary, so-called nicotine/amylose 24 h patches are produced with the following structure:

- 35 – transparent covering sheet of a polymer laminate,
- amylose film produced according to the invention, or reservoir of active substance such as the nicotine mentioned, polyglucan/TPS mixture containing 35% glycerol,
- annular adhesive layer, and

– multilayer protective laminate layer.

Materials for producing the polymer laminate, the adhesive layer and the protective laminate layer are generally known.

5

Test "plasters" normally  $7 \text{ cm}^2$  in size are cut out of said layer structure and used for the release test.

**Test design:**

10

Sotax AT7 dissolution apparatus with extraction cells (complies with USP XXIV)

Release medium: citrate/phosphate buffer pH 5.9; 900 ml.

15

Release temperature  $32^\circ\text{C}$

Online detection via a Perkin-Elmer Lambda 20 UV/VIS spectrophotometer.

20

UV detection: 290 nm.

✓  
The appended fig. 4 shows the cumulative in vitro release of nicotine from the nicotine/amylose 24 h patch and from the amylose/TPS matrix patch.

25

The release profile normally approximates to the Higuchi square-root law for matrix patches.

In place of nicotine it is possible to use a number of other pharmaceutical active substances for transdermal administration in the form, for example, of sheets or of so-called plasters.

30

**Example 9: Extruded pellets for oral administration of active substances**

35

Once again, a poly( $\alpha$ -1,4-D-glucan)/TPS polymer mixture is used as matrix for extruded pellets for oral administration of active substances according to the principle of multiple unit dosage forms.



5 Firstly, once again a sheet is produced in analogy to the amylose/TPS film which contained active substances as constituent for transdermal administration. However, only potential active substances suitable for oral use are incorporated into the polymer melt and extruded as sheet. The sheet obtained in this way is cut into strips about 1-2 mm wide and then cut up further to result in pieces of sheet about 1 mm<sup>2</sup> in size. These pieces obtained in this way, containing the pharmaceutical active substance, are compressed in tablet form or else packed into hard gelatin capsules.

10 The advantage of these so-called multiple unit dosage forms is that drug formulations which disintegrate in vivo rapidly into many subunits are obtained in this way. If a single unit dosage form, such as, for example, a conventional tablet is employed, the disintegration and thus the release of active substance is not so readily reproducible. It is possible by using  
15 pellets formulated with a combination of suitable pharmaceutical excipients or measures to achieve approximately zero order kinetics of release of active substance (for example Beloc-Zok). The release of active substance from pellets can be controlled via their geometry and administration form (tablet or capsule) by using poly( $\alpha$ -1,4-D-glucan) in combination for  
20 example with thermoplastic starch. The use of other excipients is not absolutely necessary.

The pellets or cut pieces can be packed into a capsule which can be provided with a coating resistant to gastric juice. The cut pieces or pellets  
25 can, however, also themselves receive a coating resistant to gastric juice by appropriately coating the extruded sheet with materials resistant to gastric juice. This can take place, for example, by coextrusion of multilayer sheets, in which case the layer in the middle is chosen to be the amylose/TPS layer containing the pharmaceutical active substance for oral  
30 uses. If these pellets or cut pieces are not packed into a capsule, they are normally compressed to a tablet as already mentioned above. This can in turn be provided with a coating for resistance to gastric juice or controlling the release of active substance.

### 35 **Example 10: Production of an agrochemical formulation**

In analogy to the production of a transdermal therapeutic system in example 8, initially once again one part of poly( $\alpha$ -1,4-D-glucan) is mixed with two parts of thermoplastic starch in the melt in an extruder at about

170°C, each of the two materials containing 35% glycerol as plasticizer. The polymer melt is then cooled to about 140°C, and bensulfuron-methyl (Mw = 396.4) as agrochemical active substance, and about 5% water, are added and then the resulting agrochemical polymer melt is extruded to give  
5 broad sheets by profile extrusion.

The sheet obtained in this way is then reduced in size by chopping to form particles.

10 The particles produced in this way can then be applied outside, for example at a dosage of about 30-100 g per hectare. The great advantage of the use of these amylose film particles containing the agrochemical active substance is that good dosage is possible and the release takes place with a delay. It is moreover possible to adapt the delayed release via  
15 the loading of active substance depending on the purpose of use. Although the loading of active substance in the present example is only 5%, greater loadings of active substance of up to 50% are, of course, perfectly possible.

20 The possible applications and uses of the thermoplastic poly( $\alpha$ -1,4-D-glucan) and of the thermoplastic polymer mixtures containing poly( $\alpha$ -1,4-D-glucan), described above, are, of course, only examples for illustrating the present invention. The invention is, of course, not confined to the applications mentioned or to the active substances, process parameters,  
25 polymer component partners to poly( $\alpha$ -1,4-D-glucan) etc. mentioned in the examples; on the contrary, it can be supplemented or modified in any desired way by adding further components, by choosing other process parameters etc.

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### New Patent Claims

1. A thermoplastic polymer mixture at least comprising poly( $\alpha$ -1,4-D-glucan) with a degree of polymerization of at least 40, and a plasticizer.
- 10 2. The thermoplastic polymer mixture at least comprising poly( $\alpha$ -1,4-D-glucan) as claimed in claim 1 with a degree of polymerization of > 50, and a plasticizer.
- 15 3. A thermoplastic polymer mixture at least comprising poly( $\alpha$ -1,4-D-glucan) with a degree of polymerization of at least 50 to 56, and a plasticizer.
- 20 4. The thermoplastic polymer mixture at least comprising poly( $\alpha$ -1,4-D-glucan) as claimed in either of claims 1 or 2 with a degree of polymerization of > 60, and a plasticizer.
- 25 5. The thermoplastic polymer mixture at least comprising poly( $\alpha$ -1,4-D-glucan) as claimed in any of claims 1, 2 or 4 with a degree of polymerization not exceeding 300, and a plasticizer.
6. The polymer mixture as claimed in any of the preceding claims, at least comprising another polymer which is melt-processable.
- 30 7. The polymer mixture as claimed in claim 6, where the other polymer is physiologically tolerated and/or biocompatible.
8. The polymer mixture as claimed in claim 7 which comprises a vinyl compound and/or a polyalkanoate as other polymer.
- 35 9. The polymer mixture as claimed in claim 8, which comprises a copolymer of vinyl acetate or vinyl acrylate with ethylene or polyethylene/vinyl alcohol as vinyl compound, and/or an aliphatic polyester as polyalkanoate.

10. The polymer mixture as claimed in at least one of the preceding claims, additionally comprising native starch or chemically modified starch or physically modified starch.  
5
11. The polymer mixture as claimed in claim 10, additionally comprising thermoplastic starch.
12. The polymer mixture as claimed in claim 11, wherein the mixture  
10 comprises thermoplastic starch which is obtainable by mixing native starch or a starch derivative with a plasticizer in the melt with a water content of > 5% by weight based on the starch/plasticizer mixture.
13. The polymer mixture as claimed in at least one of the preceding  
15 claims, which comprises as plasticizer for poly( $\alpha$ -1,4-D-glucan) and/or the other polymer and/or the starch at least one substance from the following list: sorbitol, glycerol and its oligomers and condensation products, DMSO, succinic acid, citric acid  
20 monohydrate, maleic acid and/or tartaric acid.
14. The polymer mixture as claimed in at least one of the preceding  
25 claims, wherein the content of starch such as, in particular, thermoplastic starch is between 20 to 80% by weight based on the polymer content, including polyglucan and, where appropriate, other melt-processable polymers.
15. The polymer mixture as claimed in at least one of the preceding  
30 claims, wherein the content of poly( $\alpha$ -1,4-D-glucan) is 20 to 80% by weight based on the polymer content, including the starch and, where appropriate, other melt-processable polymers.
16. The polymer mixture as claimed in at least one of the preceding  
35 claims, additionally comprising between 2 to 20% by weight of a complexing agent for poly( $\alpha$ -1,4-D-glucan).
17. The polymer mixture as claimed in at least one of the preceding claims, additionally comprising active substances selected from the

following list: pesticides, fungicides, insecticides, herbicides, fertilizers, pharmaceutical and/or cosmetic active substances.

- 5 18. The use of the polymer mixture as claimed in at least one of the preceding claims as thermoplastic carrier matrix for taking up at least one active substance selected from the following list: pesticides, fungicides, insecticides, herbicides, fertilizers, pharmaceutical and/or cosmetic active substances.
- 10 19. A process for preparing a thermoplastic polymer mixture as claimed in at least one of the preceding claims, which comprises initially melting poly( $\alpha$ -1,4-D-glucan) and adding to the latter at least 20% by weight of a plasticizer at 170°C.
- 15 20. A process for preparing a thermoplastic polymer mixture as claimed in at least one of the preceding claims, which comprises initially melting poly( $\alpha$ -1,4-D-glucan) and adding to the latter at least 30% by weight of a plasticizer at 170°C.
- 20 21. The process as claimed in claim 19 or 20, wherein the molten and plasticized poly( $\alpha$ -1,4-D-glucan) is mixed with at least one other melt-processable polymer in the melt at a temperature in the range from 140°C to 180°C.
- 25 22. The process as claimed in claim 21, wherein the mixing in the melt takes place in an extruder, the residence time in the extruder being 1 to 5 min at 50 to 200 revolutions per minutes, preferably 100 rpm, and with a work introduced for plasticizing and mixing per kg of poly( $\alpha$ -1,4-D-glucan) of 0.2 to 0.4 kWh.
- 30 23. The process as claimed in claim 21 or 22, wherein the melt is cooled to a temperature in the region of < 150°C and mixed with an agriculturally useful or cosmetic and/or pharmaceutical active substance, once again in the melt.
- 35 24. The process as claimed in claims 21 to 23, wherein the melt obtained in this way is extruded to a sheet or injection molded to a thermoplastic article, in which sheet or in which molded article the

thermoplastic polymer mixture comprising poly( $\alpha$ -1,4-D-glucan) and the other polymer serves as carrier matrix, and the agriculturally useful, cosmetic and/or pharmaceutical active substance is present in the form of a filler.

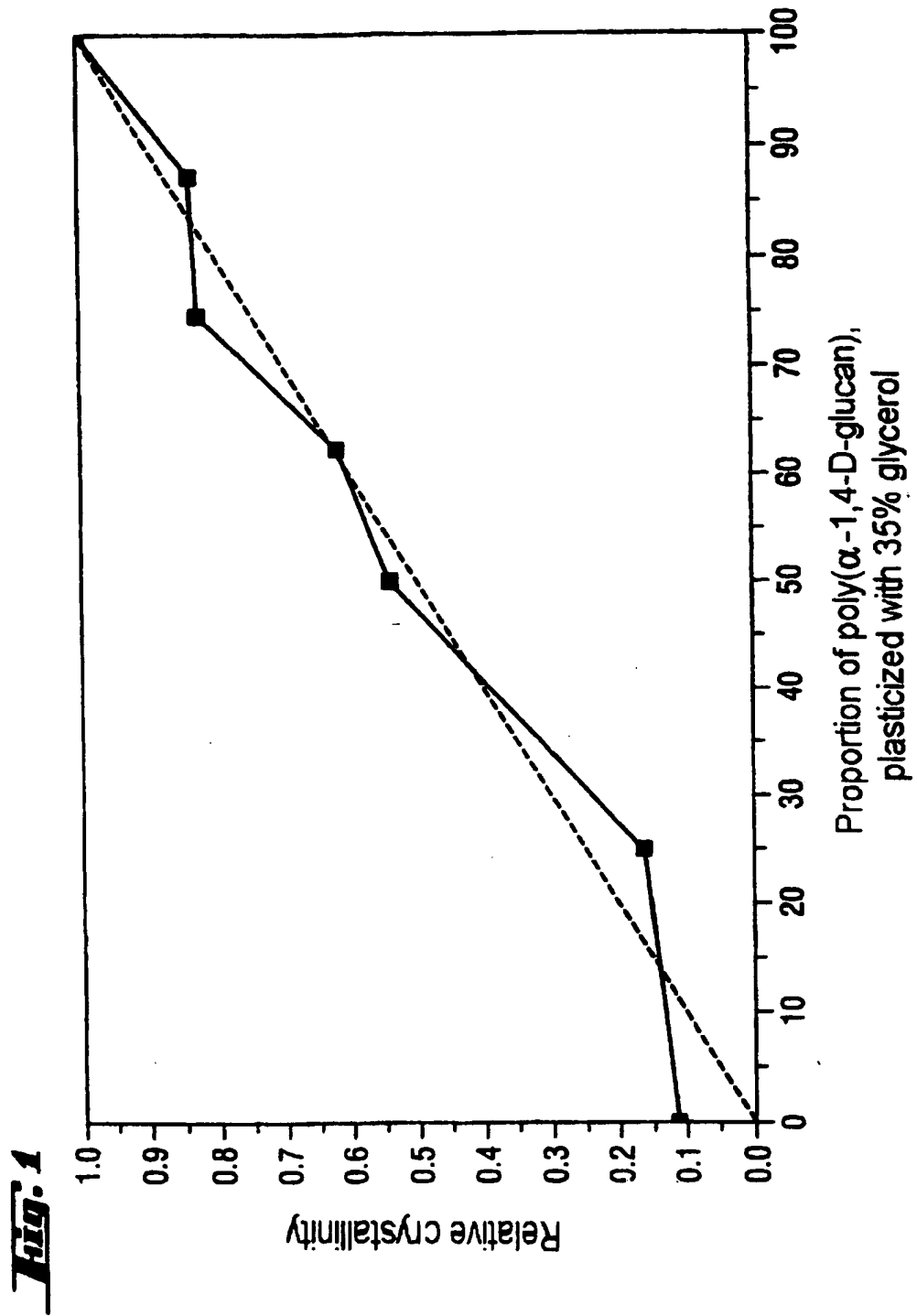
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25. The process as claimed in claim 24, wherein the extruded sheet is further processed to, for example, transdermal or agriculturally useful systems or, comminuted in tablet form or packed into capsules, is converted into a form which can be administered.

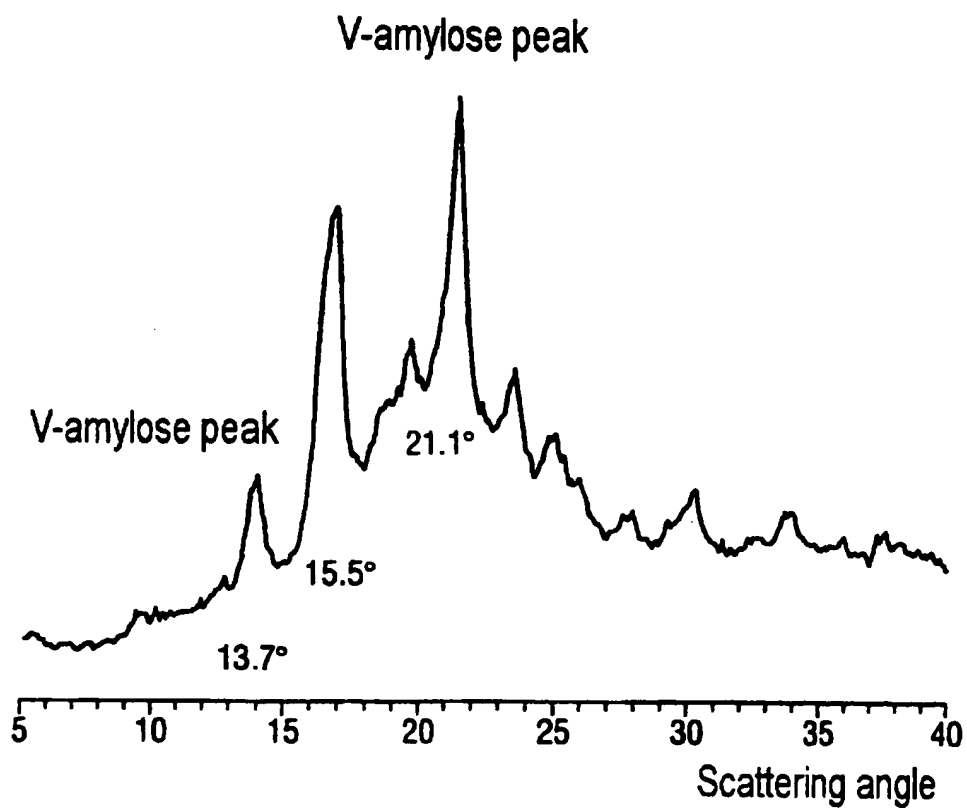
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26. The process as claimed in either of claims 24 or 25, wherein the thermoplastic molded article is further processed to a subcutaneous processing form.

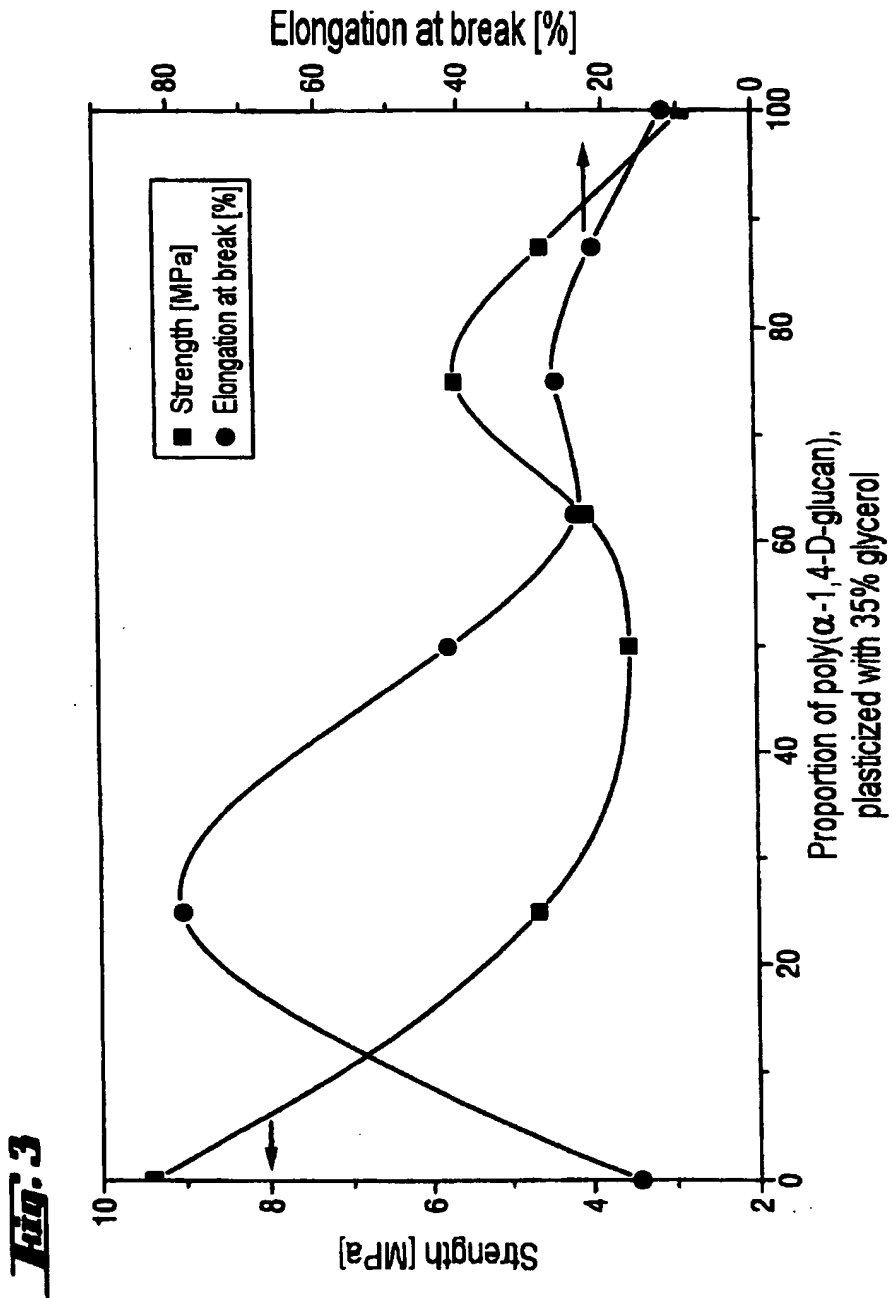
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Ottawa, Canada  
Patent Agents



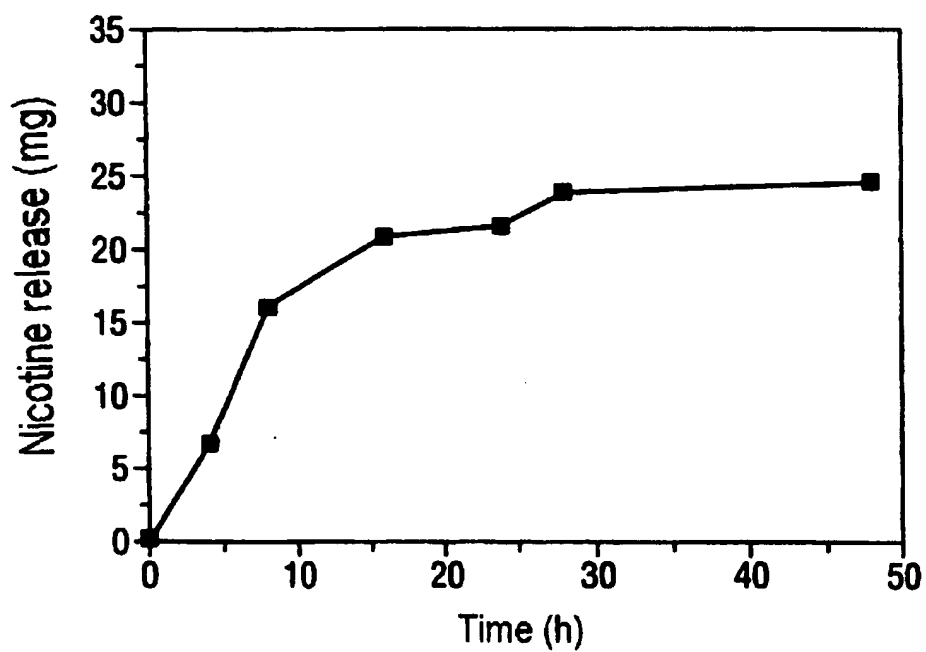
**Fig. 2: X-ray spectrum of poly( $\alpha$ -1,4-D-glucan) with 35% glycerol**







**Fig. 4: Cumulative in vitro release of nicotine from amylose matrix patches**



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